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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,219	03/11/2004	Matilde Bustos De Abajo	U 015070-8	3487

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,219	ABAJO ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-27* is/are pending in the application.

4a) Of the above claim(s) *9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response to the restriction requirement received on 9/6/06 has been entered. Claims 1-8 have been canceled and new claims 12-27 have been added. Claims 9-27 are pending in the instant application. Claims 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/6/06. Claims 12-27 are currently under examination in the instant application. An action on the merits follows.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on 9/6/06 is acknowledged. The traversal is on the ground(s) that the claims meet the unity requirement of PCT Rule 13.1, and that according to PCT Rule 13.2 the inventions share a common inventive concept which is the effects of cardiotrophin-1. The applicant further argues that since no lack of unity was made in the International phase, the U.S.P.T.O. should give deference to the views of the EPO.

This is not found persuasive because the instant application is a National phase application filed under 371. The instant application is U.S. application which claims benefit under 35 U.S.C. 120 to International application PCT/ES02/0045. As such, unity of invention and PCT Rules 13.1 and 13.2 do not apply to this application. Restriction in U.S. applications is

governed by 35 U.S.C. 121, see also 37 CFR 1.141 and 1.142. The restriction requirement mailed on 7/31/06 followed proper restriction practice under 35 U.S.C. 121. As such, it is further noted that applicant's citation of *Caterpillar Tractor Co. v. Commissioner of Patents and Trademarks*, 231 USPQ 590 (E.D. VA 1986) which discusses issues of unity in national phase application is not on point. Finally, the restriction of record clearly sets forth reasons why the administration of nucleic acids versus the administration or proteins constitute independent and distinct inventions. The previous office action stated:

> Inventions I and II are related as products which share an alleged common utility of manufacturing a composition with various intended uses in the treatment of hepatic conditions but the common utility is not linked to a substantial structural feature. The products in this relationship are distinct if either or both of the following can be shown: (1) that the products encompass embodiments that are not required to perform the common utility or (2) that the products as claimed can be used to perform another utility. In this case, a cardiotrophin-1 (CT-1) polypeptide is chemically, structurally, and functionally distinct from a polynucleotide encoding CT-1. Further, polypeptides and nucleic acids have substantially different modes of activity. Thus, the products do not share a substantial structural feature. Further, the CT-1 polynucleotides can be used to produce the CT-1 protein in tissue culture, or can be used in in vitro nucleic acid binding assays or PCR. Thus, for the reasons set forth above, the search for each invention is not co-extensive and it would place an undue burden on the examiner to search and examine both inventions together.

Thus, for reasons of record as discussed in detail above, the requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claims 12-19 and 27 are objected to as encompassing subject matter withdrawn from consideration in view of applicant's election of the invention of Group II. The claims continue to

specifically recite the administration of either cardiotrophin-1 (CT-1) or a polynucleotide that encodes CT-1. The applicant has elected the administration of cardiotrophin for examination. It is suggested that applicant's amend the claims to reflect the elected subject matter under examination.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use, as applicant's specification does not follow the preferred layout.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino

acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

It is further noted that the listing of references on pages 3-5 in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of stimulating hepatic regeneration, methods of preventing liver damage, and methods of treating intrahepatic tumors comprising administration of an effective amount of cardiotrophin-1 (CT-1) to a patient. The claims further recite wherein

the patient has chronic liver disease, hepatitis, cirrhosis, or has had hepatectomy or liver transplant.

The specification provides a brief discussion of known CT-1 activities, including binding to the CT-1 receptor and activation of various intracellular signals. The specification further states that based on their observation that the gene of CT-1 is overexpressed during hepatic regeneration following partial hepatectomy, the present invention proposes and claims the use of CT-1 to stimulate hepatic regeneration in essentially all circumstances including surgical resections, damage to the liver by chemical or biological agents, or inflammation, liver transplant, or alcoholic, viral, metabolic, or immunologic hepatic cirrhoses. The remainder of the specification, however, is limited to working examples which focus exclusively on the administration of a recombinant replication defective adenoviral vector encoding CT-1 (Ad-CT-1). While these working examples provide evidence that transfection of hepatocytes with the recombinant virus and subsequent expression of CT-1 in the transfected hepatocytes enhances hepatic proliferation following partial hepatectomy in normal rats and can inhibit hepatocyte apoptosis and necrosis caused by Con A, anti-Fas, and, TNF-alpha/DGal, the working examples do not provide any guidance regarding the administration of CT-1 polypeptide, or the administration of Ad-CT-1 for stimulating hepatic regeneration in patients with hepatitis or cirrhoses caused by alcohol, viruses, metabolic disorders, or autoimmunity.

The specification fails to provide an enabling disclosure for the therapeutic administration of CT-1 polypeptide to stimulate hepatic regeneration in patients with various liver conditions and diseases, including hepatitis, cirrhosis, or liver transplantation. The specification further fails to provide an enabling disclosure for using CT-1 -polypeptide to treat

intrahepatic tumors. As discussed above, the specification is largely directed to the administration of a recombinant adenovirus encoding CT-1. The specification mentions the use of CT-1 polypeptide on page 6, and provides a method of producing recombinant CT-1 protein in bacteria on page 9. However, this is the extent of the disclosure concerning the administration of CT-1 protein provided by the specification. The specification fails to provide any guidance regarding pharmaceutical compositions for the administration of CT-1 to patients, dosages of CT-1 which constitute an "effective amount" of CT-1 to prevent liver damage or stimulate hepatic regeneration, or routes of protein administration which are effective to deliver the protein to the liver. The specification further fails to provide any guidance as to the half-life of the protein under physiological conditions or teach the details of the treatment regimen for delivery of the "effective amount" of CT-1, i.e. a single dose of CT-1, or multiple doses on the same day or spread of several days. As such, the specification does not provide sufficient guidance for the administration of an "effective amount" of CT-1 to achieve any of the claimed effects, including the prevention of liver damage, stimulation of hepatic regeneration, or treatment of intrahepatic tumors. Please note that the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997). (emphasis added).

Furthermore, the specification's working examples using recombinant adenovirus do not overcome the lack of disclosure regarding the administration of CT-1 protein. The working examples teach the intravenous administration of Ad-CT-1. However, administration of Ad-CT-1 is not equivalent or correlative with the administration of CT-1 protein. Recombinant adenovirus has a natural tropism for the liver, such that intravenous injection can result in delivery of the vector to the target organ. CT- protein has no such tropism or targeting activity. Further, viral infection of hepatocytes results in transient continuous expression of the protein in the target cells for at least several days, if not longer, thereby reducing issues relating to protein half-life and clearance. Furthermore, dosages for the administration of adenoviral vectors and the dosages for protein administration are not comparable. As noted above, the specification provides no guidance concerning the dosage, the route of administration, or the number of protein administrations required to achieve any therapeutic effect on hepatic regeneration or liver damage. Further, the prior art teaches that intraperitoneal administration of CT-1 protein results in numerous effects on the host, including trophic effects on the heart, liver, thymus, and spleen, alterations in blood chemistry, and changes in platelets and red blood cells (Jin et al. (1996) Cytokine, Vol. 8 (12), 920-926). In view of the art recognized broad spectrum of effects of CT-1 protein administration, it would have required undue experimentation to determine the route of administration and amount of CT-1 protein capable of stimulating liver regeneration or preventing liver damage without causing without causing potentially devastating side effects in other organ systems.

The specification further fails to provide an enabling disclosure for treating chronic or acute liver diseases including hepatitis or cirrhosis by administering CT-1 protein. The prior art

at the time of filing teaches that alcoholic hepatitis and cirrhosis are life-threatening diseases for which few treatments are currently available. While Narayanon Melon et al. teaches that stimulation of liver regeneration represents a future potential treatment approach for hepatitis and cirrhosis, Narayanon Melon et al. teaches that, "[t]his concept has been examined in patients with alcoholic hepatitis by treatment with insulin and glucagon, which is thought to stimulate liver regeneration. However, the results have been discouraging.", and that "[t]herapies using more selective hepatotrophic agents, such as hepatocyte growth factor, are compelling but remain untested.." (Narayanon Melon et al. (2001) Mayo Clinic Proceedings, Vol. 76 (10), 1021-1029, see page 1027). It is noted that CT-1 is not hepatoselective as it effects many organs and cells. Thus, the prior art at the time of filing establishes that therapy of chronic liver diseases such as alcoholic hepatitis and cirrhosis by stimulating liver regeneration was considered unpredictable. Applicant's disclosure does not overcome the art recognized unpredictability for treating these diseases by stimulating liver regeneration as the specification does not provide any specifics as to protein dosage or administration or provide any evidence for therapeutic liver regeneration in patients with hepatitis or cirrhosis.

The specification further fails to provide an enabling disclosure for treating intrahepatic tumors with CT-1. The specification is silent as to the treatment of intrahepatic tumors using CT-1. The only mention of tumors occurs on page 2, which states that cardiotrophin has been previously employed in the diagnosis and treatment of tumors, referencing WO 00/43790. However, this document in fact teaches away from using CT-1 protein to treat tumors. WO 00/43790 teaches that tumors, such as lung and colon tumors, overexpress CT-1 and discloses the treatment of these tumors by inhibiting CT-1 activity using antibodies against CT-1 and CT-1

antagonists (WO 00/43790, pages 2-3). As such, the prior art teaches the exact opposite of the instant methods as claimed and thus provides evidence of unpredictability for treating any tumor, including a hepatic tumor using CT-1. It is further noted that as the specification clearly teaches the anti-apoptotic activity of CT-1, the skilled artisan would not have predicted that an anti-apoptotic protein would have any beneficial effect in killing tumors cells or in inhibiting their growth. Thus, due to the anti-apoptotic properties of CT-1, the teachings of the prior art to inhibit CT-1 activity to treat tumors, and the complete lack of guidance in the specification for using CT-1 to treat intrahepatic tumors, it would have required undue experimentation to practice the methods of treating tumors as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12, 14, 20, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Jin et al. (1996) Cytokine, Vol. 8 (12) 920-926. The applicant claims methods for stimulating hepatic regeneration and methods of preventing damage to a liver comprising administration of an effective amount of cardiotrophin-1 to a patient in need thereof.

Jin et al. teaches the i.p. administration of 2ug of cardiotrophin twice a day for 14 days resulting in liver growth (Jin et al., page 921-922, Table I and Figure 2, and page 925). While the

mice receiving the cardiotrophin were normal mice, the specification does not provide any specific definition for "in need thereof" such that any "patient" meets this claim limitation. It is further noted that while Jin et al. does not specifically teach the administration prevents liver damage, the method steps taught by Jin et al. for inducing liver growth are identical to those claimed. The applicant is reminded that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. *In re Woodruff*, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Thus, by teaching the exact methods steps as the instant claims, Jin et al. anticipates claim 12, 14, 20, and 22.

Claims 13, 15-10, 21, and 23-27 appear to be free of the prior art of record. While the prior art teaches the administration of cardiotrophin-1 to stimulate liver growth, see Jin et al. above, the prior art of record does not teach or suggest administering cardiotrophin-1 to stimulate hepatic regeneration in patients with chronic liver diseases, cirrhosis, or hepatitis, or in patients following hepatectomy or liver transplant.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all

official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

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PRIMARY EXAMINER